Reprinted from *Pediatrics*, Vol. 15, No. 6
June, 1955

NEONATAL ANOXIA

I. A Study of the Relation of Oxygenation at Birth to Intellectual Development

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IN THE PAST 25 years, studies of the relationship of mental or motor development to the events which took place at birth have followed 1 of 4 approaches: a) the observation of a neurological or psychological defect in a child and tracing his history back to the time of birth;[1-5] b) the notation of central nervous system symptoms or trauma at the time of birth and following the survivors for several years;[6-13] c) the observance of asphyxia or apnea at birth with similar follow-up visits,[14,15] and d) the recording of clinical events at the birth of an unselected series of infants and tracing their future development.[16,17] In this study, a fifth approach has been used—that of recording objective data relating to oxygenation in an unselected series of infants and following their subsequent course.

Recognizing the possible introduction of bias into retrospective analyses we planned in 1947 a forward-looking study to determine the outcome of children who were and who were not anoxic at birth. From April, 1948, to August, 1950, blood samples were taken from infants born at Sloane Hospital for Women, as soon as possible after birth and at several intervals thereafter. These infants were followed by the staff of Babies Hospital for 4 years to observe mental development, cerebral palsy or other neurological abnormality.

MATERIAL AND METHODS

Four hundred four infants, born on the ward service between 9 A.M. and 5 P.M. on weekdays, became the subject of this study. There was no other selection of cases. Cord blood samples were collected in 235 infants and heel blood samples in all infants; collection times were carefully recorded and 1 chemist

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Supported by funds from The Rockefeller Foundation.

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Grateful acknowledgment is made to Dr. Richard L. Day for assistance in planning technical details, and to Drs. Duncan A. Holaday and John W. Fertig and Miss Marjorie Bellows for statistical advice.

(Submitted for publication December 21, 1954.)

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TABLE I

HEEL BLOOD VS. FEMORAL ARTERY BLOOD DRAWN SIMULTANEOUSLY FROM NEWBORN INFANTS

Oxygen Content in vol. per cent	
Heel	*Femoral artery*
13.2	12.7
8.2	10.1
15.0	14.6
10.9	10.2
11.8	11.2
10.5	11.3

carried out all the analyses for oxygen content and capacity. A total of 1787 determinations were made. An average of 3.9 samples per infant was collected from 1 minute to 3 hours after birth. In addition to the obstetrical and medical information on the mother's chart, notes were made in the delivery room as to the time from delivery of the chin to the first breath (breathing time), to the first audible cry (crying time), the type of resuscitation employed, if any, and the use of oxygen therapy. Neonatal notes included observations of chest retraction, persistent cyanosis and convulsions. Later, between the ages of 21 and 34 months (mean, 26.7 months) Gesell developmental ratings were determined, and between the ages of 28 and 55 months (mean, 47.6 months) Stanford-Binet (Form L) and Seguin Form Board tests were applied.

Cord blood samples were obtained from a long, isolated segment of cord which was doubly clamped. The cord was clamped initially as soon as the infant was born, without "stripping" or waiting for pulsation of the umbilical arteries to cease. A second pair of clamps was applied near the placenta as soon as it was delivered. The blood sample was obtained from the umbilical vein by incising it under oil in a special collecting cup. The time of collecting the sample was usually between 5 and 10 minutes after birth of the infant.

The choice of the heel as a source of capillary blood was made after due deliberation. Femoral artery or temporal artery puncture was considered to be too difficult for repeated sampling. The frequent persistent cyanosis of the feet is well known, but appears to be unrelated to capillary blood oxygenation if the puncture is made deeply enough. The use of capillary blood as a reflection of arterial oxygenation was first documented by Lundsgaard and Möller[18] who reported the comparison of adult finger tip blood with that of the radial artery. In 1942, Smith and Kaplan[19] pointed out the usefulness of the heel as a source of blood for oxygenation studies in infants, and subsequently others have followed their example.[20,21] Satisfactory correlation was obtained in studies by Lowry, Smith, and Cohen[22] who compared finger tip blood of medical students with that of their radial arteries in 13 cases. In 1944, Lilienthal and Riley[23] also found close correlation when comparing blood from the heated ear lobe and brachial artery in 11 cases. In the present study the oxygen content of heel blood was compared with that of simultaneously drawn femoral artery blood in 6 infants between 5 and 7 minutes after birth (Table I). No notes were made as to whether an infant's heel was cyanotic or pink at the time of collection of the blood. With a single exception, the samples compared satisfactorily as to oxygen content. Instances in which the oxygen content of capillary (heel) blood was found to be higher than that of arterial blood in the same patient may be presumed to reflect the combined errors of the sampling and analytical methods.

A No. 11 Bard-Parker blade was inserted briskly into the heel, which was then immersed in a collecting cup which had been rinsed with a dilute heparin solution and filled with mineral oil at room temperature. Two to 3 ml. samples were obtained without undue pressure on the leg.

Oxygen content was determined by the microgasometric method of Roughton and Scholander.[24] Although this test is not altogether precise, control analyses with and without anesthetic agents in the blood sample demonstrate that its sensitivity is ± 1 vol. per cent when analyses made by the Van Slyke and Neill method[25] are used as standard. With a range of oxygen content values from 1.1 to 27.4 vol. per cent, it is easily apparent that the Roughton-Scholander method of oxygen analysis is ade-

TABLE II

DISTRIBUTION ACCORDING TO RACE

Negro	46%
White	40%
Puerto Rican	12%
Oriental	2%

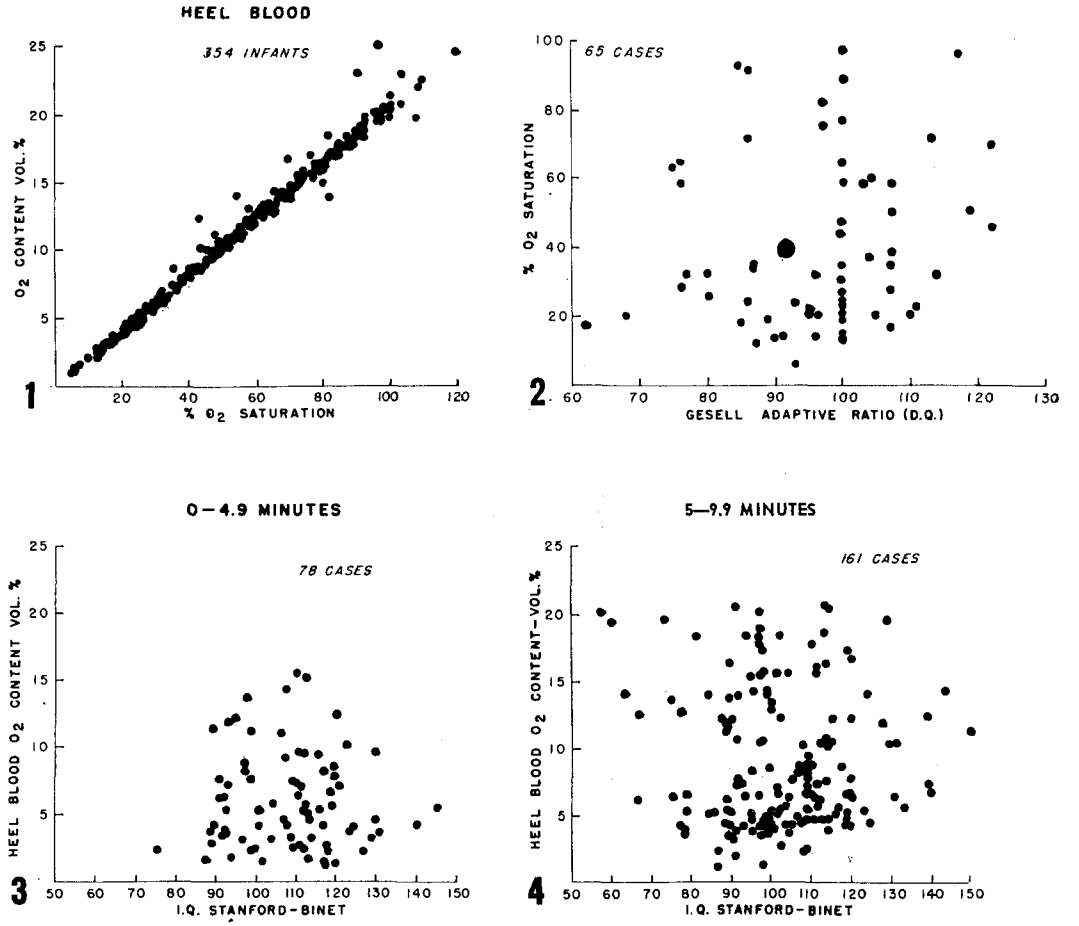


FIG. 1. Relation between oxygen content and oxygen saturation of 354 samples of heel blood drawn between 5 and 10 minutes after birth.

FIG. 2. Relation between neonatal oxygen saturation and adaptive performance (developmental quotient as measured by Gesell adaptive rating at age 21 to 34 months) in 65 cases. The oxygen saturation plotted for each case is the lowest value found during the first 10 minutes after birth.

FIG. 3. Relation between oxygen content of heel blood in the first 5 minutes after birth and I.Q. measured by Stanford-Binet test given at ages 3 to 5 years, in 78 cases. The blood oxygen value for each case is the lowest determination obtained between birth and age 4.9 minutes.

FIG. 4. Relation between oxygen content of heel blood in the second 5 minutes after birth and I.Q. measured by Stanford-Binet test given at age 28 months to 5 years, in 161 cases.

quate for the study undertaken.

During the first part of the study, blood samples were measured for their oxygen content alone. So far as the metabolism of brain cells is concerned, with only partial saturation of arterial hemoglobin the partial pressure of oxygen in equilibrium with hemoglobin is determined by the oxygen content of the hemoglobin and by the shape of the dissociation curve; but variations in hemoglobin concentration of individual blood samples are not taken into account when oxygen content alone is measured. In the latter part of the study both oxygen content and capacity were measured so that the percentage saturation of a given sample could be calculated. Analysis of the correlation between oxygen content and oxygen saturation was made in 354 blood samples for which both values were available (Fig. 1). The close correlation found ($r = .993$) clearly establishes the practicality of using either dimension interchangeably.

The racial characteristics of the mothers of the patients are listed in Table II, parity in

TABLE III

PARITY

Primipara	43%
Multipara	57%

Table III and type of delivery in Table IV. Thirty-two per cent of the mothers were over 30 years old. There were 3 sets of twins. Twenty-seven per cent of the mothers presented some special obstetrical problem and 29 per cent an antenatal medical problem. Membranes had been ruptured for more than 24 hours in 6 per cent. The duration of the first stage of labor was over 12 hours in 25 per cent, and the second stage over 1 hour in a similar number. Six per cent of the infants were premature, as judged by birth weight under 2500 gm.

Tables V, VI, and VII list the types of pain relief used. One-third of the mothers who received regional anesthesia were given supplemental inhalation anesthesia. Three-quarters of the anesthesias were administered by the members of the Department of Anesthesiology and the remainder by obstetrical residents or medical students.

RESULTS

Of the 404 patients studied at the time of birth, 275 (68 per cent) returned for psychological tests (Table VIII).

Sixty-five patients were assessed according to the Gesell Developmental Schedule with its 4 component ratings for motor, adaptive, language and personal-social behavior. In comparing Gesell developmental quotients (D.Q.) with neonatal blood oxygenation we have used only the adaptive ratio, (adaptive age/chronological age) × 100, since it is believed to be less influenced by environmental variables than are the other 3 criteria. When D.Q. values were plotted against the lowest saturation of heel blood oxygen found in the first 10 minutes after birth, the results showed no significant correlation (Fig. 2: r = .04).

TABLE IV

TYPE OF DELIVERY

Spontaneous vertex	50%
Low forceps	40%
Cesarean section	8%
Breech	2%

TABLE V

ANTEPARTUM SEDATIVE AND ANALGESIC MEDICATION

None	5.0%
Meperidine	88.0%
Scopolamine	88.0%
Barbiturate	51.0%
Morphine	1.5%

Two hundred sixty-five Stanford-Binet tests were applied, of which 22 were discarded because of lack of cooperation or language difficulty. There were thus available 243 I.Q. values for comparison with measurements of neonatal blood oxygen made in the same subjects. No significant correlation was found between I.Q. and either oxygen content or oxygen saturation of blood collected at any time during the first 3 hours of life (Table IX; Figs. 3–9). Patients with the lowest postnatal oxygen values showed a wide scatter of subsequent I.Q. determinations, and a similar result was found with high neonatal oxygen values. The 22 patients with blood oxygen content below 3 vol. per cent during the first 10 minutes of life showed no consistent depression of I.Q. (average 104.7), and the 34 patients whose blood oxygen content was not observed to fall below 14 vol. per cent during the first 2 hours after birth likewise had a wide scatter of I.Q. values (average 100.9). This result is not unexpected because of the low correlation coefficient in every group sampled. Additional examples of nonsignificant correlation result from the analysis of 13 patients with I.Q. values of 80 or less, who showed an average oxygen content of 9.8 vol. per cent, and of 33 patients with I.Q. of 120 or more, who had an average oxygen content of 8.6 vol. per cent.

TABLE VI

PRIMARY ANESTHESIA TECHNIC FOR DELIVERY

None	1%
Local or pudendal block	4%
Spinal block	9%
Caudal and epidural	3%
Inhalation	80%
No record	3%

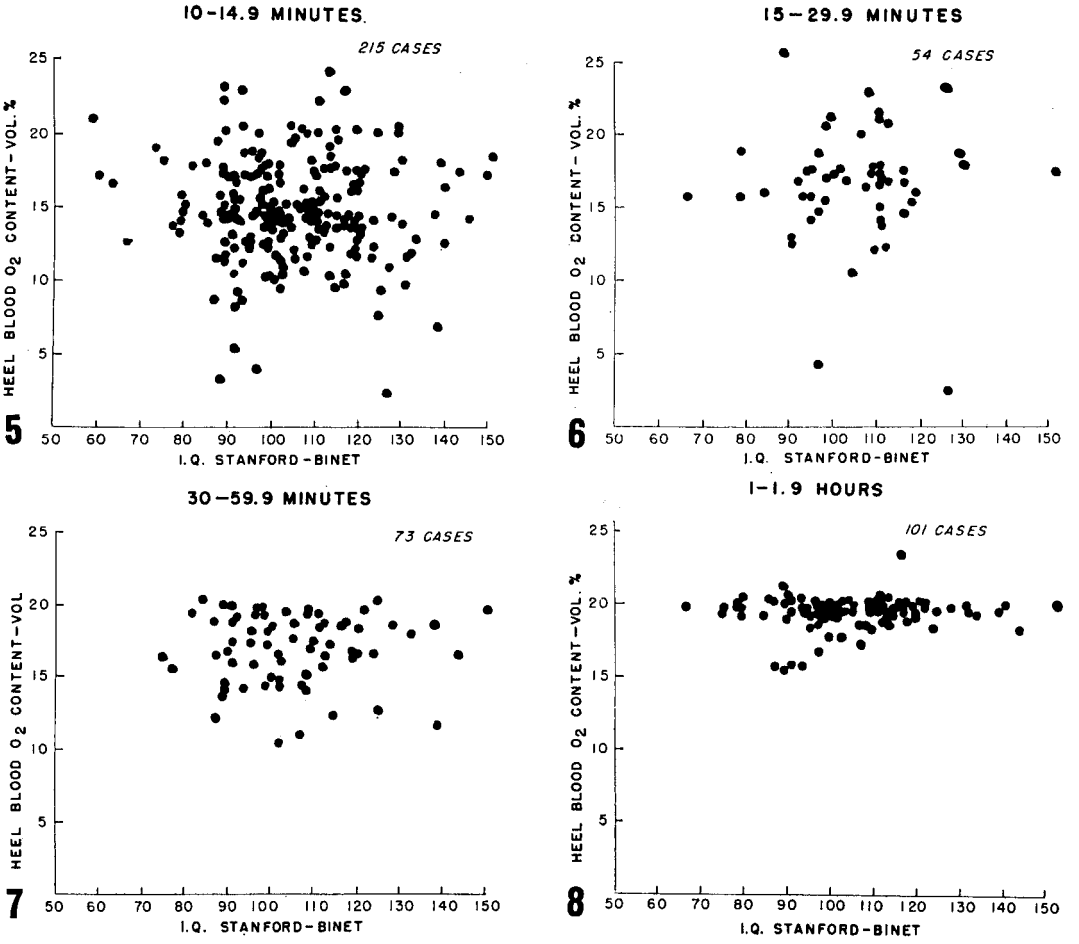


FIG. 5. Relation between oxygen content of heel blood in the third 5 minutes after birth and I.Q. measured by Stanford-Binet test given at age 28 months to 5 years, in 215 cases.

FIG. 6. Relation between oxygen content of heel blood in the second quarter-hour after birth and I.Q. measured by Stanford-Binet test given at ages 3 to 5 years, in 54 cases.

FIG. 7. Relation between oxygen content of heel blood in the second half-hour (30-59.9 minutes) after birth and I.Q. measured by Stanford-Binet test given at age 28 months to 5 years, in 73 cases.

FIG. 8. Relation between oxygen content of heel blood in the second hour (1 to 1.9 hours) after birth and I.Q. measured by Stanford-Binet test given at age 28 months to 5 years, in 101 cases.

NEONATAL COMPLICATIONS

Six infants were noted to have moderate chest retraction during the first 2 days of life. Three could not be followed, but in the 3 infants with satisfactory follow-up visits the lowest postnatal oxygen saturation and the corresponding Stanford-Binet I.Q. value at approximately 47 months were, respectively, 26 per cent with 123 I.Q., 37 per cent with 91 I.Q., and 35 per cent with 106 I.Q. Another infant, a premature who weighed 1800 gm. at birth and who exhibited severe chest retraction for 2 days, had an oxygen saturation of 12 per cent 10 minutes after birth in spite of attempted oxygen therapy. At 43 months, the I.Q. was 86. Clinically, the diagnosis appeared to be hyaline membrane syndrome, but with recovery.

Five infants had persistent cyanosis in spite of oxygen saturations of 21, 36, 42, 69, and 87 per cent, a range of values which supports the observations of other workers[26,27] that in the immediate postnatal

TABLE VII

PRIMARY INHALATION AGENTS

Nitrous oxide	32%
Cyclopropane	13%
Ether	55%

period cyanosis does not necessarily parallel oxygen saturation as measured. At 4 years of age, the intelligence quotients of 3 of these patients were 92, 98 and 138.

Seven infants exhibited convulsive manifestations during the neonatal period; in this group the range of oxygen saturation within 10 minutes of birth was 23 to 77 per cent and the I.Q.'s of the 3 subsequently tested were 92, 102 and 118. One of the 7 died at 2 years of pneumonia, and the behavior of 1 of the 3 children who did not return for testing was reported by the social service worker to indicate retardation.

One child developed convulsions associated with hyperthermia at 4 years of age but was not mentally retarded.

NEUROLOGICAL COMPLICATIONS

Among the 279 patients who either returned for testing or died (Table VIII) there were 2 examples of mongolism and 6 instances of severe mental retardation as measured by an I.Q. score of less than 70 in the Stanford-Binet test (Table X). One patient in the latter group also suffers from muscular dystrophy. In addition, 1 patient with microcephaly who died at 2 years of age was almost certainly retarded in mental development, and another patient with cerebral palsy who scored only 21 on the Gesell adaptive rating and who could not even be subjected to the Stanford-Binet test was likewise presumed to have suffered intellectual impairment. Thus, in all, there were 10 certain or highly probable instances of mental retardation at the defective level among 279 individuals or a frequency of 3.6 per cent—a frequency which might represent chance distribution without requiring any additional explanatory factor in the circumstances of neonatal adjustment to extrauterine oxygenation.[28] Moreover, the neonatal oxygenation of these mentally retarded patients, as gauged again by the lowest value for heel blood oxygenation measured in the first 10 minutes after birth, did not differ significantly (M = 49 per cent, S.D. = 28) from that of the entire population studied.[29]

TABLE VIII

RESULTS OF 4-YEAR FOLLOW-UP

Neonatal deaths	2
Death between 1 mo. and 3 yr.	2
Completely lost to follow-up	54
Did not return, probably not lost	71
Children tested	275
	404

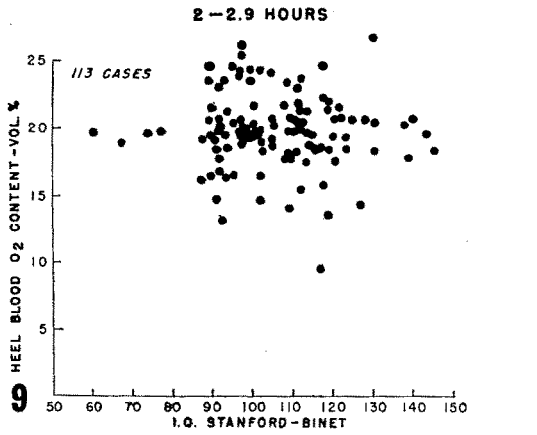
DISCUSSION

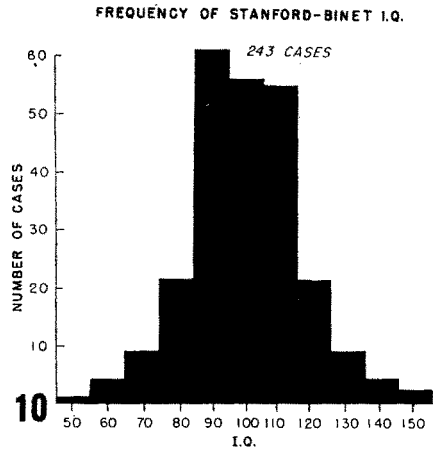
The group of children subjected to Stanford-Binet intelligence rating was large enough to provide a representative scatter of

TABLE IX

COMPARISON OF OXYGEN CONTENT OF HEEL BLOOD COLLECTED AT VARIOUS INTERVALS AFTER BIRTH, WITH STANFORD-BINET I.Q. MEASURED AT 3 TO 5 YEARS OF AGE

Time of Sample	*No. Cases*	*Mean O_2 Cont. (vol. %)*	*S.D. O_2 Cont. (vol. %)*	*Mean I.Q.*	*S.D. I.Q.*	*Corr. Coeff. (r)*
Birth–4.9 min.	78	6.1	3.6	107.9	13.5	+.05
5– 9.9 min.	161	9.1	5.2	102.0	15.9	−.02
10– 14.9 min.	215	15.0	3.2	104.5	14.9	−.30
15– 29.9 min.	54	16.6	3.4	104.6	15.1	−.06
30– 59.9 min.	73	17.1	2.4	104.5	15.1	+.02
60–119.9 min.	101	19.4	1.6	105.6	18.2	−.16
120–179.9 min.	113	19.8	3.9	104.9	15.1	+.04





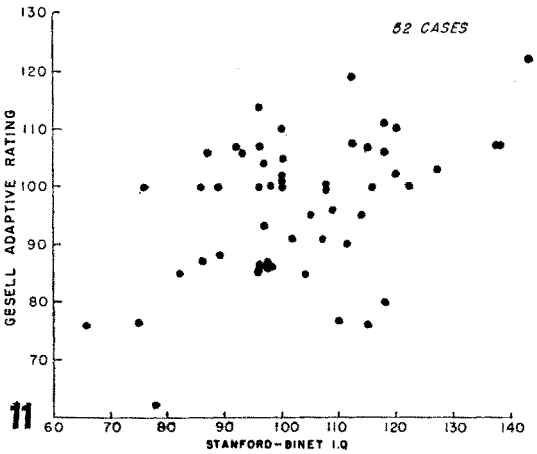


FIG. 9. Relation between oxygen content of heel blood in the third hour (2 to 2.9 hours) after birth and I.Q. measured by Stanford-Binet test, given at age 3 to 5 years, in 113 cases.

FIG. 10. Frequency distribution of 243 Stanford-Binet tests.

FIG. 11. Comparison of the Gesell developmental evaluation $\frac{\text{(adaptive age} \times 100)}{\text{(chronological age)}}$ with Stanford-Binet I.Q. in 52 individuals. The Gesell adaptive rating was made at 21 to 34 months; Stanford-Binet tests were applied between the ages of 28 months and 5 years.

I.Q. values, with a range of 57 to 152, even after attrition of the original population of newborn infants from loss of clinic contact.

TABLE X

CEREBRAL ABNORMALITIES

Neurological Condition	*Lowest Oxygen Sat.*	*Stanford-Binet Intelligence Quotient*
Mongolism	28%	could not be tested
Mongolism	15%	could not be tested
Mental retardation	95%	57
Mental retardation	87%	60
Mental retardation	69%	63
Mental retardation	29%	66
Mental retardation	20%	68
Cerebral Palsy with mental retardation	55%	could not be tested (Gesell D.Q.=21)
Microcephaly with mental retardation	23%	died at 2 years
Muscular dystrophy	65%	66

Indeed, the distribution of I.Q. values (Fig. 10) shows a close approximation to the normal curve. The basis of original selection being purely temporal, related only to the hour and day of birth, there is no reason to suspect bias in regard either to level of neonatal oxygenation or to subsequent mental development; and there is likewise no reason to believe that the group who eventually returned for evaluation of intelligence included more than its share of the extremes of either neonatal oxygenation or I.Q. One would therefore suppose that any direct correlation between neonatal anoxia and ultimate mental development ought to be revealed in the analysis of the data.

Difficulties of blood collection made it impossible to get samples in all infants at planned intervals after birth, but by accurate timing and recording and by inclu-

sion of a large enough number of observations, it was believed that correct inferences might be drawn regarding relationships between levels of blood oxygen content or saturation in the immediate postnatal period and subsequent mental development. In the measurement of blood oxygen levels, systematic errors of 2 sorts might be introduced: 1) the inclusion in the blood sample of significant amounts of inhalation anesthetics, and 2) loss of oxygen from the arterial blood when heel blood is used. Reasons have already been expressed for believing each of these errors to be unimportant. Moreover, even if summation of the two should in a particular instance result in a significant reduction of blood oxygen as measured below the level existing in that patient's arteries, the direction of the error would not interfere with the detection of other instances in which neonatal anoxia might be causally related to subsequent lowering of I.Q. We recognize that the circumstances of our study permitted us to throw no light on disturbances of fetal circulation, including changes in oxygenation of the infant's blood, which might have been in operation during labor or, in fact, at any time before birth. Anoxia occurring at such a time could conceivably injure cerebral cells, thus setting the stage for delayed intellectual development, and yet remain undetected by the observations gathered in the course of this investigation.

The predictive value of the Gesell developmental ratings has not been extensively studied, and we therefore hesitated to use these tests as a criterion of intellectual development. At the same time, it has been of interest to apply Gesell tests to individual children included in the study and to compare the results with Stanford-Binet ratings made at an older age level in the same subjects. The correlation coefficient ($r = +.195$) casts doubt on the reliability of the adaptive behavior component of Gesell tests as a predictive index if Stanford-Binet tests constitute the frame of reference (Fig. 11). Since ratings in the 4 separate components of the Gesell Developmental Schedule—motor, adaptive, language and personal-social behavior—usually correlate quite closely among themselves when applied to individual subjects, our observations would warrant caution in using these tests, applied before the age of 3 years, as the basis for prognosticating ultimate mental competence. This caution is justified even though the predictive limitations of Stanford-Binet tests themselves are recognized.

SUMMARY

In a study designed to measure the effect of delayed oxygenation of newborn infants' blood on intelligence in later life, capillary blood oxygen content or saturation was measured at various intervals in the first 3 hours after birth, and in the same individual subjects intelligence was later assessed by Stanford-Binet test. Technically satisfactory data for both variables—blood oxygen content and I.Q.—were available in 243 randomly selected subjects. The distribution of postnatal blood oxygen values shows wide scattering during any finite time interval arbitrarily marked off in the first hour following delivery, but averages for the first 3 successive 5-minute periods of independent respiration rise progressively, the average for the second 15-minute period is higher than for the first, the average for the second half-hour higher than for the first, and by the second hour most infants have stabilized at average adult levels of blood oxygen content. The distribution of intelligence quotients for the group as a whole conforms closely to that of a normal curve.

No significant correlation was found between levels of blood oxygen content measured in the first 3 hours after birth and intelligence as gauged by Stanford-Binet testing in early childhood.

An incidental finding of this study is the meager value of the Gesell developmental rating of adaptive behavior, measured at approximately 2 years of age, in predicting the Stanford-Binet intelligence quotient as measured at approximately 5 years of age.

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SPANISH ABSTRACT

Anoxia Neonatal. I. Estudio de la Relación entre Oxigenación al Nacimiento y Desarrollo Intelectual

La relación del desarrollo mental o motor a los sucesos del nacimiento se ha enfocado en los últimos 25 años de cuatro maneras: observación de defectos neurológicos o psicológicos en un niño y estudio de su vida en forma retros-

pectiva; observación de trauma o manifestaciones neurológicas centrales al nacimiento y vigilancia posterior del paciente durante varios años; observación de cianosis y apnea y vigilancia posterior similar; por último, anotación de datos clínicos al nacimiento de una serie no seleccionada de niños y vigilancia de su desarrollo futuro. En el presente trabajo se ha echado mano de un quinto camino: anotación de datos objetivos relacionados con la oxigenación al nacimiento de una serie no seleccionada de niños y estudio del curso subsecuente de los pacientes.

En 1947 los autores trazaron un plan para analizar los datos hallados en niños con anoxia o sin ella al nacimiento; de abril, 1948, a agosto, 1950, tomaron muestras de sangre de estos niños inmediatamente al nacer y a diversos intervalos, y los vigilaron durante 4 años en cuanto a desarrollo mental y presencia de parálisis cerebral o de alguna otra anormalidad neurológica. El estudio se basó en 404 recién nacidos; se tomó sangre del cordón en 235 de los niños y del talón en todos ellos, practicándose 1787 determinaciones de contenido y capacidad de oxígeno, con un promedio de 3.9 muestras por niño desde un minuto a tres horas después del nacimiento. La sangre capilar y venosa dieron dieron cifras similares de acuerdo con el método microgasométrico de Roughton y Scholander. En esta forma los autores creyeron tener datos para estudiar el efecto del retardo de oxigenación de la sangre sobre la inteligencia posterior basada en las pruebas de Gessel practicadas entre los 21 y 34 meses y de Stanford-Binet y de Seguin entre los 28 y 55.

De los 404 pacientes estudiados al nacer, 275 regresaron para las pruebas psicológicas. No se encontró relación significativa entre el cociente de inteligencia y el contenido de oxígeno y concentración de oxígeno en la sangre obtenida en cualquier momento durante las primeras tres horas de la vida. Hubieron 10 casos seguros o probables de retardo mental en 279 individuos, dando una frecuencia de 3.6%, quizá representativa de distribución al azar que no requiera un factor adicional explicativo de las circunstancias de ajuste neonatal a la oxigenación extrauterina; además la oxigenación neonatal de estos pacientes retardados no difirió en forma significativa de la de la población estudiada.

Se lograron obtener en 243 niños datos técnicamente satisfactorios para ambos variables (oxígeno sanguíneo y cociente de inteligencia). Aunque el contenido en oxígeno sanguíneo durante el período neonatal mostró amplias variaciones en cualquier momento dentro de la primera hora después del nacimiento, los promedios para los tres primeros períodos consecutivos de 5 minutos de respiración independiente se elevaron progresivamente; el promedio fué luego superior en el segundo período de 15 minutos que para el primero, así como el de la segunda media hora que el de la primera; en la mayoría de los niños se alcanzó el nivel promedio de adultos en contenido de oxígeno sanguíneo alrededor de la segunda hora. El cociente de inteligencia se distribuyó para el grupo total de acuerdo con una curva normal.

No se encontró ninguna relación significativa entre los niveles de oxígeno sanguíneo en las primeras tres horas de la vida y el grado de inteligencia medido por las pruebas de Stanford-Binet, durante la primera infancia. Incidentalmente los autores señalan el escaso valor en los niños de dos años de la prueba de Gessel para la conducta de adaptación como guía de predecir el cociente de inteligencia de Stanford-Binet a los 5 años de edad.